REMARKS

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Restriction requirement/election

Election, with traverse, of the claims of Group I (encompassing claims 1, 17, 18, and 56-61), directed to polypeptides and compositions, is acknowledged. Applicants thank the Examiner for acknowledging that, upon allowance of the product claims, rejoinder of process claims commensurate in scope with the allowed product claims will be considered.

II. Obviousness-type double patenting over U.S. Patent No. 6,001,624

Claims 1, 17, 18, and 56-61 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1 and 2 of U.S. Patent No. 6,001,624 (hereinafter "the '624 patent"). Applicants request that the requirement for submission of a Terminal Disclaimer with respect to the '624 patent be held in abeyance until such time that there is an indication of allowable subject matter.

III. New matter rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 17, 58, and 61 were rejected under 35 U.S.C. § 112, first paragraph, because the recitation of "fragments of SEQ ID NO:1 that comprises residues R6 through V23 with adenylate kinase activity" is allegedly new subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention (Office Action, May 14, 2003; page 5, § 4). This rejection is traversed.

In determining whether there is adequate support in the specification to convey to a skilled artisan that the inventors had possession of the claimed invention, the M.P.E.P. provides that "[t]he subject matter of the claim need not be describe literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." M.P.E.P. § 2163.02. Thus, there is no

requirement for the specification to literally recite the phrase "a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has adenylate kinase activity, and wherein the fragment comprises residues R6 through V23 of SEQ ID NO:1." All that is required is that the specification **reasonably** conveys that the inventors were in possession of the claimed invention.

The instant application provides examples of fragments of SEQ ID NO:1 which are biologically active. For example, the specification discloses functional characteristics of particular portions of the SEQ ID NO:1 polypeptide:

> "The N-terminal sequence between residues R6 and V23 constitutes a positively charged, amphipathic region that may be important for targeting HMAK to the mitochondrial membrane. Positively charged residues at R6, R9, and K20 are known to be important for this function and are shared by all four molecules shown [HMAK, cow AK3, rat AK3, and human AK3]. The consensus sequence GXXGXGK important for mononucleotide binding in AK is present in HMAK beginning at [G14] and is shared by the three AK3 proteins." (Specification at page 11, lines 22-28)

Thus, the specification explicitly discloses fragments of SEQ ID NO:1 comprising amino acid residues R6 through V23. In addition, the specification discloses that the consensus sequence GXXGXGK is found at amino acid residues G14 through K20 (the recitation of "G13" rather than "G14" in the specification is an obvious and unintentional typographical error; it is obvious from the Sequence Listing and Figures 1A and 2A that the first glycine residue of the GXXGXGK consensus sequence is located at position 14 rather than 13). Since consensus sequence spanning residues G14 through K20 is encompassed within the portion of SEQ ID NO:1 comprising residues R6 through V23, and since the consensus sequence is "important for mononucleotide binding in AK," one of skill in the art would understand that residues R6 through V23 of SEQ ID NO:1 play a role in the adenylate kinase activity of the SEQ ID NO:1 polypeptide (HMAK). Thus, the specification provides an example of "fragments of SEQ ID NO:1 having adenylate kinase activity" by reciting the portion of SEQ ID NO:1 comprising residues R6 through V23. Therefore, based on the disclosure of the specification, one of skill in the art would reasonably understand that the recited fragments having adenylate kinase activity were fully supported by the application as filed, and its parent applications.

Furthermore, the instant application claims priority to U.S. patent application 08/829,027 (hereinafter "the '027 application"). As filed, claim 1 of the '027 application reads as follows:

1. A substantially purified mitochondrial adenylate kinase comprising the amino acid sequence of SEQ ID NO:1 or fragments thereof.

Thus, at the time of filing of the '027 application (March 31, 1997), the '027 application explicitly disclosed adenylate kinases comprising fragments of SEQ ID NO:1. In other words, the '027 application disclosed fragments of SEQ ID NO:1 having adenylate kinase activity. Based on original claim 1 of the '027 application, fragments of SEQ ID NO:1 having adenylate kinase activity are not new matter in the instant application.

Since the specification of the '027 application disclosed fragments of SEQ ID NO:1 having adenylate kinase activity, and since the specification provides an example of such a fragment by disclosing that the consensus sequence found within residues R6 through V23 of SEQ ID NO:1 plays a role in adenylate kinase activity, the recited "fragments of SEQ ID NO:1 comprising R6 through V23 and having adenylate kinase activity" are not new matter.

For at least the reasons above, the subject matter of claims 1, 17, 58, and 61 is fully supported by the specification of the application as filed, and withdrawal of this rejection is therefore requested.

Furthermore, to expedite prosecution, claim 1 has been amended such that the recited fragments, comprising residues R6 through V23 of SEQ ID NO:1, "bind mononucleotides." Support for this amendment can be found in the specification at, for example, page 11, lines 22-28. For example, the specification explicitly discloses that the GXXGXGK consensus sequence which is contained within the portion of SEQ ID NO:1 bounded by residues R6 through V23 is "important for mononucleotide binding in AK" (Specification, e.g., at page 11, lines 26-27). In addition, the specification provides an assay to measure the binding of molecules to the SEQ ID NO:1 polypeptide or biologically active fragments thereof (Specification, e.g., at page 47, line 26 to page 48, line 3). By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include fragments comprising residues R6 through V23 of SEQ ID NO:1 which have adenylate kinase activity. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claim 1, as amended, and its dependent claims, recite patentable subject matter. Therefore, withdrawal of this rejection, at least with respect to claim 1 and its dependent claims, is requested.

IV. Rejections of claims 1 and 58 under 35 U.S.C. § 102(b)

Claims 1 and 58 were rejected under 35 U.S.C. § 102(b) because the recited polypeptide fragments, comprising residues R6 through V23 of SEQ ID NO:1 and having adenylate kinase activity, are allegedly anticipated by Isogai et al. (SPTREMBL database, accession Q9NPB4). The Office Action asserts that the subject matter of the claims cannot benefit from the filing dates of its parent applications because the subject matter is not supported by the parent applications (Office Action, May 14, 2003; page 6, § 5). This rejection is traversed.

Applicants maintain that one of skill in the art would reasonably understand that the claimed subject matter is supported by the parent applications from which the instant application claims priority, as discussed above in § III. Thus, the subject matter of the claims is entitled to the benefit of the priority date of U.S. application 08/829,027 (March 31, 1997), and Isogai et al. do not anticipate the claimed invention. For at least these reasons, withdrawal of this rejection is requested.

Furthermore, to expedite prosecution, claim 1 has been amended such that the recited fragments, comprising residues R6 through V23 of SEQ ID NO:1, "bind mononucleotides." Support for this amendment can be found in the specification at, for example, page 11, lines 22-28. For example, the specification explicitly discloses that the GXXGXGK consensus sequence which is contained within the portion of SEQ ID NO:1 bounded by residues R6 through V23 is "important for mononucleotide binding in AK" (Specification, e.g., at page 11, lines 26-27). In addition, the specification provides an assay to measure the binding of molecules to the SEQ ID NO:1 polypeptide or biologically active fragments thereof (Specification, e.g., at page 47, line 26 to page 48, line 3). By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include fragments comprising residues R6 through V23 of SEQ ID NO:1 which have adenylate kinase activity.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claim 1, as amended, recites patentable subject matter. Therefore, withdrawal of this rejection, at least with respect to claim 1, is requested.

V. Rejections under 35 U.S.C. § 103(a)

Claims 17 and 61 were rejected under 35 U.S.C. § 103(a) because the claimed compositions comprising the recited polypeptide fragments are allegedly obvious over Isogai et al. (SPTREMBL database, accession Q9NPB4). This rejection is traversed.

This rejection is based on the allegation that the polypeptide taught by Isogai et al. anticipates the recited polypeptide fragments. As discussed above in §§ III and IV, the subject matter of the claims is entitled to the benefit of the priority date of U.S. application 08/829,027 (March 31, 1997), and Isogai et al. do not anticipate the recited polypeptide fragments. Therefore, Isogai et al. cannot be used as a reference against the claimed subject matter, and the Patent Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103. For at least these reasons, withdrawal of this rejection is requested.

Furthermore, to expedite prosecution, claim 1 (from which claims 17 and 61 depend) has been amended such that the recited fragments, comprising residues R6 through V23 of SEQ ID NO:1, "bind mononucleotides." Support for this amendment can be found in the specification at, for example, page 11, lines 22-28. For example, the specification explicitly discloses that the GXXGXGK consensus sequence which is contained within the portion of SEQ ID NO:1 bounded by residues R6 through V23 is "important for mononucleotide binding in AK" (Specification, e.g., at page 11, lines 26-27). In addition, the specification provides an assay to measure the binding of molecules to the SEQ ID NO:1 polypeptide or biologically active fragments thereof (Specification, e.g., at page 47, line 26 to page 48, line 3). By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include compositions comprising fragments which comprise residues R6 through V23 of SEQ ID

NO:1, and which have adenylate kinase activity. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claims 17 and 61, as amended, recite patentable subject matter. Therefore, withdrawal of this rejection is requested.

VI. Rejections of claims 1, 17, 57, and 60 under 35 U.S.C. § 102(b)

Claims 1, 17, 57, and 60 were rejected under 35 U.S.C. § 102(b) because the recited polypeptide variants, which are at least 95% identical to SEQ ID NO:1 and have adenylate kinase activity, are allegedly anticipated by Yamada et al. (J. Biol. Chem., 1989, 264:19192-19199). The Office Action asserts that "[e]ven though Yamada's sequence does not currently display 95% or higher identity with SEQ ID NO:1, using slightly different sequence analysis parameters, can result in an identity of at least 95% or higher of said sequence to SEQ ID NO:1 of this invention" (Office Action, May 14, 2003, page 8, § 9). This rejection is traversed.

To support an anticipation rejection, there is a burden on the Patent Office to provide convincing proof that the references teach the claimed invention. In this case, the Patent Office has not met this burden. The Office Action has **not** provided convincing evidence that the AK3 polypeptide taught by Yamada et al. is the same as the polypeptide variants recited by the claims. Instead, the Office Action states that the use of "slightly different sequence analysis parameters" "**can** result in identity of at least 95% or higher of said sequence to SEQ ID NO:1" (Office Action, May 14, 2003; page 8, § 9; emphasis added). Based on the possibility that identity greater than 95% can be achieved by altering the sequence analysis parameters, the Office Action concludes that the claims are anticipated. This is improper.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102(b), "the reference must teach every aspect of the claimed invention either explicitly or implicitly." M.P.E.P. § 706.02. However, the Patent Office has not provided any evidence to show that the alteration of sequence analysis parameters would lead to identity greater than 95% between the AK3 polypeptide of Yamada et al. and SEQ ID NO:1. The Patent Office must provide a rationale or evidence tending to show that

the properties of the claimed subject matter are taught by the references used in an anticipation rejection. For at least this reason, withdrawal of this rejection is requested.

Furthermore, the Office Action is incorrect in asserting that identity greater than 95% can be achieved between the AK3 polypeptide of Yamada et al. and SEQ ID NO:1 by altering the sequence analysis parameters. Note that Figures 2A and 2B of the application show a sequence alignment between the SEQ ID NO:1 polypeptide, the AK3 polypeptide of Yamada et al. (labeled as g217576), and two other polypeptides. The sequence alignment between SEQ ID NO:1 and the AK3 polypeptide is the best possible alignment between these two polypeptides because these polypeptides each have 227 amino acids, there is a perfect 1:1 correspondence between the residues of SEQ ID NO:1 and the residues of AK3, and there are no gaps in the alignment. In other words, each amino acid residue of SEQ ID NO:1 has one corresponding amino acid residue in AK3. Any different alignment between these two polypeptides would not be as good because such an alignment would require gaps in the alignment, thus destroying the perfect 1:1 correspondence between the residues of the polypeptides.

Based on this best possible alignment between SEQ ID NO:1 and AK3, there are 208 amino acid residues which are identical between the sequences. Using simple arithmetic, the division of 208 by 227 (the total number of residues in each polypeptide) gives a value of 91.6% for the percent identity between SEQ ID NO:1 and AK3. This is the highest possible value which can be obtained for the identity between AK3 and SEQ ID NO:1, based on the best possible alignment between these two sequences as presented in Figures 2A and 2B. Even if one considered the two "X" amino acids of SEQ ID NO:1 to be identical to their counterparts in AK3 (Applicants maintain that this is not the case), these two polypeptides would still be only 92.5% identical (210 identical residues divided by 227 total residues). Based on these calculations, it would not be possible to obtain a value of 95% identity between SEQ ID NO:1 and AK3 by altering the sequence analysis parameters. Although the Patent Office asserts that AK3 and SEQ ID NO:1 have 94% identity, the Office Action has not provided any evidence to support this value for percent identity. Without evidence that alteration of

sequence analysis parameters could result in sequence identity of 95% or greater between SEQ ID NO:1 and the AK3 polypeptide of Yamada et al., there is no credible support for this rejection.

For at least the above reasons, withdrawal of this rejection is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

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Limited Recognition (37 C.F.R. § 10.9(b)) attached
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